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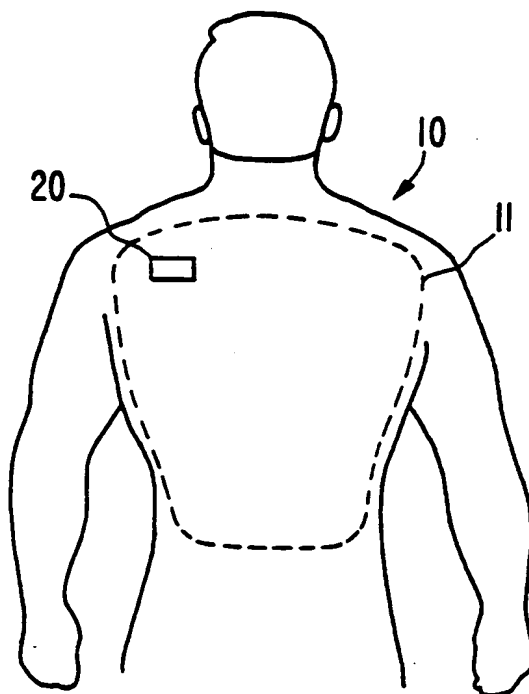
(57) Abstract

An improved method for delivering a drug or beneficial agent transdermally to humans by iontophoresis is provided. The method includes selecting and iontophoretically delivering the drug through a skin site (11) which optimizes the transdermal delivery rate of the drug while minimizing inter-patient variability in skin resistance.

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IMPROVED IONTOPHORETIC DELIVERY METHOD

TECHNICAL FIELD

5   This invention relates to an improved method for delivering an agent transdermally by iontophoresis. More specifically, this invention relates to a method of increasing the efficiency of an iontophoretic delivery device and to an improved method of using such a device.

10

BACKGROUND ART

Iontophoresis, according to Dorland's Illustrated Medical Dictionary, is defined to be "the introduction, by means of

15   electric current, of ions of soluble salts into the tissues of the body for therapeutic purposes." Iontophoretic devices have been known since the early 1900's. British patent specification No. 410,009 (1934) describes an iontophoretic device which overcame one of the disadvantages of such early devices known to the art at

20   that time, namely the requirement of a special low tension (low voltage) source of current which meant that the patient needed to be immobilized near such source. The device of that British specification was made by forming a galvanic cell from the electrodes and the material containing the medicament or drug to

25   be transdermally delivered. The galvanic cell produced the current necessary for iontophoretically delivering the medicament. This ambulatory device thus permitted iontophoretic drug delivery with substantially less interference with the patient's daily activities.

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More recently, a number of United States patents have issued in the iontophoresis field, indicating a renewed interest in this mode of drug delivery. For example, Vernon et al U.S. Patent No. 3,991,755; Jacobsen et al U.S. Patent No. 4,141,359; Wilson U.S.

35   Patent No. 4,398,545; and Jacobsen U.S. Patent No. 4,250,878

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disclose examples of iontophoretic devices and some applications
thereof. The iontophoresis process has been found to be useful in
the transdermal administration of medicaments or drugs including
lidocaine hydrochloride, hydrocortisone, fluoride, penicillin,
5   dexamethasone sodium phosphate and many other drugs. Perhaps the
most common use of iontophoresis is in diagnosing cystic fibrosis
by delivering pilocarpine salts iontophoretically. The
pilocarpine stimulates sweat production; the sweat is collected
and analyzed for its chloride content to detect the presence of
10 the disease.

In presently known iontophoretic devices, at least two
electrodes are used. Both of these electrodes are disposed so as
to be in intimate electrical contact with some portion of the skin
15 of the body. One electrode, called the active or donor electrode,
is the electrode from which the ionic substance, medicament, drug
precursor or drug is delivered into the body by iontophoresis.
The other electrode, called the counter or return electrode,
serves to close the electrical circuit through the body. In
20 conjunction with the patient's skin contacted by the electrodes,
the circuit is completed by connection of the electrodes to a
source of electrical energy, e.g., a battery. For example, if the
ionic substance to be driven into the body is positively charged,
then the positive electrode (the anode) will be the active
25 electrode and the negative electrode (the cathode) will serve to
complete the circuit. If the ionic substance to be delivered is
negatively charged, then the negative electrode will be the active
electrode and the positive electrode will be the counter
electrode.
30

Alternatively, both the anode and cathode may be used to
deliver drugs of opposite charge into the body. In such a case,
both electrodes are considered to be active or donor electrodes.
For example, the positive electrode (the anode) can drive a
35 positively charged ionic substance into the body while the

●   ●

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negative electrode (the cathode) can drive a negatively charged
ionic substance into the body.

It is also known that iontophoretic delivery devices can be
5   used to deliver an uncharged drug or agent into the body. This is
accomplished by a process called electroosmosis. Electroosmosis
is the volume flow of a liquid (e.g., a liquid containing the
uncharged drug or agent) through the skin induced by the presence
of an electric field imposed across the skin.
10

Furthermore, existing iontophoresis devices generally
require a reservoir or source of the ionized or ionizable species
(or a precursor of such species) which is to be iontophoretically
delivered or introduced into the body. Examples of such
15   reservoirs or sources of ionized or ionizable species include a
pouch as described in the previously mentioned Jacobsen U.S.
Patent No. 4,250,878, or a pre-formed gel body as disclosed in
Webster U.S. Patent No. 4,382,529. Such drug reservoirs are
electrically connected to the anode or the cathode of an
20   iontophoresis device to provide a fixed or renewable source of one
or more desired species.

Recently, the transdermal delivery of peptides and proteins,
including genetically engineered proteins, by iontophoresis has
25   received increasing attention. Generally speaking, peptides and
proteins being considered for transdermal or transmucosal delivery
have a molecular weight ranging between about 500 to 40,000
daltons. These high molecular weight substances are too large to
passively diffuse through skin at therapeutically effective
30   levels. Since many peptides and proteins carry either a net
positive or net negative charge and because of their inability to
passively diffuse through skin, they are considered likely
candidates for iontophoretic delivery.

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In particular, iontophoresis is being considered for long
term delivery (i.e., delivery for periods of longer than 24 hours)
of a number of drugs, including peptides (e.g., insulin) and
proteins. As the length of delivery increases there is a need to
5   develop small unobtrusive iontophoretic delivery devices which can
be easily worn on the skin under clothing. One example of a small
iontophoretic delivery device designed to be worn on the skin is
disclosed in U.S. Patent 4,474,570. Devices of this type are
powered by small low voltage batteries. In addition to the need
10   for developing smaller iontophoretic delivery devices, there is a
need to reduce the cost of these devices in order to make them
more competitive with conventional forms of therapy such as pills
and subcutaneous injections. One method of reducing cost is to
use even lower voltage power sources. Unfortunately, as the power
15   source voltage decreases, the drug delivery rate also decreases.
Thus, there has been a need for a method of improving the
performance characteristics, such as the amount of drug delivered
per unit of power, of iontophoretic delivery devices to enable the
use of inexpensive low-voltage power sources.
20

One method of increasing the rate at which drug is delivered
from a transdermal iontophoretic drug delivery device is to apply
the device on a skin site having optimum drug transport
characteristics. For example, Abramson and Gorin in J. Phys.
25   Chem., Vol. 44, pp 1094-1102 (1940); Burnette and Marrero, J.
Pharm. Sci., Vol. 75, pp. 738-743 (1986); and Burnette and
Ongpipattanakul, J. Pharm. Sci., Vol. 77, pp. 132-137 (1988) have
all shown that during iontophoresis, ions are preferentially
transported transdermally through shunt pathways in the skin, such
30   as sweat ducts and hair follicles. The face and scalp have the
highest density of hair follicles in humans (see Bloom and
Fawcett, A Textbook of Histology, 10th ed., W.B. Saunders Co., p
594). Abramson and Gorin have further shown that iontophoretic
transport takes place mainly through sweat duct skin pores rather
35   than hair follicle skin pores. Based on this transport mechanism,

5

one would expect that skin sites having a high density of sweat
ducts and hair follicles would be preferred sites for
iontophoresis. Table 1, taken from Rothman's: Physiology and
Biochemistry of the Skin, Chicago, University Press, p 158 (1971),
5   shows the distribution of sweat ducts in human skin.

TABLE 1

Distribution of Sweat Ducts in Human Skin

10   No. per cm^2

Palms   424

15   Soles   417

Dorsa of Hands   231

Forehead   195
20
Chest and Abdomen   176

Forearm
        Flexor aspect   174
25
        Extensor aspect   169

Dorsa of Feet   143

30   Thigh and Leg
        Medical aspect   89

        Lateral aspect   86

35   Cheek   85

Nape of Neck   65

Back and Buttocks   65
40

Based on this data and on the known mechanism for
iontophoretic drug delivery one would expect that the preferred
delivery sites would be the head, hands and feet. Surprisingly,
45   the present invention provides a method for increasing the rate at
which a drug or other beneficial agent is delivered through intact

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human skin by selecting a skin site other than that having the
highest density of sweat ducts.

DISCLOSURE OF THE INVENTION

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The present invention provides a method of enhancing the
rate at which an agent (e.g., a drug) is iontophoretically
delivered, and to an improved method of using known iontophoretic
delivery devices, by means of the intentional selection of a skin
10   site for the transdermal delivery of the agent by iontophoresis.
Use of this invention greatly increases the efficiency and
efficacy of known iontophoretic drug delivery devices.

The present invention provides a method of transdermally
15   administering a beneficial agent from an iontophoretic delivery
device to a human patient. According to the present invention,
the rate at which the beneficial agent is delivered through the
skin of the patient may be increased by selecting a site on intact
back skin of the patient and securing the donor electrode of an
20   iontophoretic delivery device in agent-delivering relation to the
selected skin site.

Any known iontophoretic delivery device may be used in
accordance with the present invention. Iontophoretic delivery
25   devices include a donor electrode assembly which includes a donor
electrode and a reservoir containing the beneficial agent to be
iontophoretically delivered. The donor electrode assembly is
adapted to be placed in agent transmitting relation to the skin or
mucosa of the patient. The device also includes a counter
30   electrode assembly adapted to be placed in electrical contact with
the skin at a location spaced apart from the donor electrode.
Further, the device includes an electric power source. The
electrodes and the power source are electrically connected and
form a closed circuit when the electrode assemblies are placed in
35   current conducting relation to the skin of the patient.

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BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a perspective view showing the site of iontophoretic delivery according to the present invention;

5

Figure 2 is a schematic view of an iontophoretic delivery device;

Figure 3 is a bar graph showing the average _in vivo_
10 electrical resistance of human skin taken from various subjects as well as the variability between the subjects; and

Figure 4 is a graph showing the flux of the drug metoclopramide through human cadaver skin taken from various sites
15 on the body of the same subject.

MODES FOR CARRYING OUT THE INVENTION

When selecting an optimum skin site for the transdermal
20 iontophoretic delivery of a drug, a number of factors are taken into consideration. First, the rate at which drug is transported through the skin should be high enough to provide therapeutically effective plasma levels of drug at the electrical current level chosen for the particular delivery system. Secondly, the
25 electrical resistance of the skin is preferably as low as possible. Thirdly, the variability between individual patients, in both the flux rate and the skin resistance, is preferably as low as possible. Fourthly, the skin site will preferably have a high tolerance to sensing the electrical current being applied by
30 the device. Fifthly, the selected skin site should have as high a resistance to skin irritation as possible. The sources of potential skin irritation include (1) adverse reaction to the drug being delivered, (2) the occlusion of the skin site by the delivery device and (3) the application of electric current by the
35 device.

8

Taking into consideration these five factors, it has
surprisingly been discovered that human back skin is an optimum
site for iontophoretic drug delivery in humans. Human back skin
is best defined with reference to Figure 1 showing a rear view of
5   a human patient 10. Back skin is defined herein as that skin
within the dotted lines 11. Figure 1 illustrates one possible
placement of an iontophoretic drug delivery device 20 on intact
back skin of human patient 10.

10   The methods of the present invention can be used to improve
the performance characteristics, such as the amount of drug
delivered per unit of power, of any known iontophoretic delivery
device including those described in U.S. Patent Nos. 4,325,367;
4,474,570; 4,557,723; 4,640,689; and 4,708,716; all of which are
15 incorporated herein by reference. Similarly, the methods of the
present invention can be used to advantage with any known
iontophoretic donor electrode assembly which is adapted to be
connected to an external power source, including those electrode
assemblies described in U.S. Patent Nos. 4,274,420; 4,391,278;
20 4,419,092; and 4,702,732; all of which are incorporated herein by
reference.

Figure 2 illustrates one example of a preferred
iontophoretic delivery device 20. Device 20 has a top layer 21
25 which contains an electrical power supply (e.g., a battery or a
series of batteries) as well as optional control circuitry such as
a current controller (e.g., a resistor or a transistor-based
current control circuit), an on/off switch, and/or a
microprocessor adapted to control the current output of the power
30 source over time.

Device 20 also includes electrode assembly 18 and electrode
assembly 19. Electrode assemblies 18 and 19 are separated from
one another by an electrical insulator 26, and form therewith a
35 single self-contained unit. For purposes of illustration, the

electrode assembly 18 will be referred to as the "donor" electrode
assembly while electrode assembly 19 will be referred to as the
"counter" electrode assembly. In this embodiment, the donor
electrode 22 is positioned adjacent drug reservoir 24 while the
5   counter electrode 23 is positioned adjacent the return reservoir
25 which contains an electrolyte. Electrodes 22 and 23 are formed
from metal foils (e.g., silver or zinc), or a polymer matrix
loaded with metal powder, powdered graphite, carbon fibers, or any
other suitable electrically conductive material. Reservoirs 24
10   and 25 can be polymeric matrices or gel matrices. Insulator 26 is
composed of a non-electrical conducting and non-ion-conducting
material which acts as a barrier to prevent short-circuiting of
the device 20. Insulator 26 can be an air gap, a non-ion-
conducting polymer or adhesive or other suitable barrier to ion
15   flow. The device 20 is adhered to the skin by means of ion-
conducting adhesive layers 27 and 28. The device 20 also includes
a strippable release liner 29 which is removed just prior to
application to the skin.

20   In a typical device 20, the drug reservoir 24 contains an
ionizable supply of the drug to be delivered and the counter
reservoir 25 contains a suitable electrolyte. Alternatively,
device 20 can contain an ionizable supply of drug in both
reservoirs 24 and 25 and in that manner both electrode assemblies
25   18 and 19 would function as donor electrode assemblies. For
example, positive drug ions could be delivered through the skin
from the anode electrode assembly, while negative drug ions could
be introduced from the cathode electrode assembly.

30   Generally, the combined skin-contacting area of electrode
assemblies 18 and 19 can range from about 1 cm^2 to greater than
200 cm^2, but typically will range from about 5 to 50 cm^2.

In accordance with the present invention, the drug reservoir
35   24 of the iontophoretic delivery device 20 must be in agent

transmitting relation with human back skin as defined by dotted
lines 11. It is not necessary, however, that the return reservoir
25 also be in electrolyte transmitting relation with human back
skin as defined by dotted lines 11, although this is greatly
5   preferred.

The method of the present invention is particularly useful
in optimizing the transdermal drug flux of iontophoretic drug
delivery devices utilizing a low-voltage power source. In
10   particular, the method of the present invention is useful in
optimizing (i) the agent transdermal delivery rate and (ii) the
amount of agent delivery per unit of power from devices powered by
a low voltage power source (e.g., a battery, or a series of
batteries, having a combined voltage in the range of about 1 to 10
15   volts).

As used herein, the expressions "agent" and "drug" are used
interchangeably and are intended to have their broadest
interpretation as any therapeutically active substance which is
20   delivered to a living organism to produce a desired, usually
beneficial, effect. In general, this includes therapeutic agents
in all of the major therapeutic areas including, but not limited
to, anti-infectives such as antibiotics and antiviral agents,
analgesics and analgesic combinations, anesthetics, anorexics,
25   antiarthritics, antiasthmatic agents, anticonvulsants, anti-
depressants, antidiabetic agents, antidiarrheals, antihistamines,
anti-inflammatory agents, antimigraine preparations, antimotion
sickness preparations, antinauseants, antineoplastics,
antiparkinsonism drugs, antipruritics, antipsychotics,
30   antipyretics, antispasmodics, including gastrointestinal and
urinary, anticholinergics, sympathomimetrics, xanthine
derivatives, cardiovascular preparations including calcium channel
blockers, beta-blockers, antiarrythmics, antihypertensives,
diuretics, vasodilators, including general, coronary, peripheral
35   and cerebral, central nervous system stimulants, cough and cold

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preparations, decongestants, diagnostics, hormones, hypnotics,
immunosuppressives, muscle relaxants, parasympatholytics,
parasympathomimetrics, proteins, peptides, polypeptides and other
macromolecules, psychostimulants, sedatives and tranquilizers.

5

The device of the present invention can be used to deliver,
in a controlled manner, the following drugs: baclofen,
betamethasone, beclomethasone, buspirone, cromolyn sodium,
dobutamine, doxazosin, droperidol, fentanyl, sufentanil,
10   ketoprofen, lidocaine, metoclopramide, methotrexate, miconazole,
midazolam, nicardipine, prazosin, piroxicam, scopolamine,
testosterone, verapamil, tetracaine, diltiazem, indomethacin,
hydrocortisone, terbutaline and encainide.

15   More preferably, the invention is useful in the controlled
delivery of peptides, polypeptides and other macromolecules
typically having a molecular weight of at least about 300 daltons,
and typically a molecular weight in the range of about 300 to
40,000 daltons. Specific examples of peptides and proteins in
20   this size range include, without limitation, LHRH, LHRH analogs
such as buserelin, gonadorelin, naphrelin and leuprolide, GHRH,
insulin, heparin, calcitonin, endorphin, TRH, NT-36 (chemical
name: N=[[(s)-4-oxo-2-azetidinyl]carbonyl]-L-histidyl-L-
prolinamide), liprecin, pituitary hormones (e.g., HGH, HMG, HCG,
25   desmopressin acetate, etc.,), follicle luteoids, αANF, growth
factor releasing factor (GFRF), βMSH, somatostatin, bradykinin,
somatotropin, platelet-derived growth factor, asparaginase,
bleomycin sulfate, chymopapain, cholecystokinin, chorionic
gonadotropin, corticotropin (ACTH), erythropoietin, epoprostenol
30   (platelet aggregation inhibitor), glucagon, hyaluronidase,
interferon, interleukin-2, menotropins (urofollitropin (FSH) and
LH), oxytocin, streptokinase, tissue plasminogen activator,
urokinase, vasopressin, ACTH analogs, ANP, ANP clearance
inhibitors, angiotensin II antagonists, antidiuretic hormone
35   agonists, antidiuretic hormone antagonists, bradykinin

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antagonists, CD4, ceredase, CSF's, enkephalins, FAB fragments, IgE
peptide suppressors, IGF-1, neurotrophic factors, parathyroid
hormone and agonists, parathyroid hormone antagonists,
prostaglandin antagonists, pentigetide, protein C, protein S,
5   renin inhibitors, thymosin alpha-1, thrombolytics, TNF, vaccines,
vasopressin antagonist analogs, alpha-1 anti-trypsin
(recombinant).

It is most preferable to use a water soluble salt of the
10   drug or agent to be delivered.

In certain cases, it may be desirable to deliver the drug or
agent with a skin permeation enhancer. The permeation enhancer
can be selected from any of a wide variety of known materials
15   capable of enhancing transdermal drug flux. Known permeation
enhancers include surfactants, alkyl substituted sulfoxides, alkyl
polyethylene glycols, lower alcohols and the permeation enhancers
disclosed in U.S. Patent Nos. 3,989,816; 4,405,616; 4,415,563;
4,424,210; and 4,722,726 which are incorporated herein by
20   reference, for example.

Having thus generally described our invention, the following
examples will further illustrate selected preferred embodiments.

25   EXAMPLE 1

The transdermal flux of metoclopramide HCl through samples
of human cadaver back skin was measured using a polycarbonate test
cell in which the skin sample to be tested is secured between a
30   donor compartment and a receptor compartment. The donor
compartment had a volume of 2 ml and was filled with an aqueous
solution of 10 wt% metoclopramide HCl. The receptor compartment
also had a volume of 2 ml and was filled with Dulbecco's phosphate
buffered saline (pH 7) sold by Gibco Laboratories, Grand Island,
35   NY. The area of the skin samples available for transport was 1.26

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cm². The test cell device was maintained at a temperature of 32°C
using an aluminum block heat exchanger. An anode comprising a
disk of silver foil having a thickness of 0.025 mm was present in
the donor compartment while a cathode comprising a sintered disk
5   of powdered silver metal and silver chloride was present in the
receptor compartment. Thus, the reduction of silver ions to
silver metal occurred at the cathode, while the oxidation of
silver to silver ions took place at the anode.

10   Human cadaver skin was used for the permeation studies.
Before securing the skin samples between the donor and the
receptor compartment of the test cell, the skin was first heat-
stripped by immersing the skin sample in water maintained at 60°C
for 90 seconds allowing the epidermis layer to be separated from
15   the dermis. Circular epidermis samples having a diameter of 2.22
cm were cut using a gasket cutting punch. The epidermis samples
were then mounted in the permeation test cell with the stratum
corneum side facing the donor compartment.

20   The electrodes of the test cell were then connected to a
Model 363 Potentiostat/Galvanostat, made by EG&G Princeton Applied
Research, Princeton, NJ, which supplied a constant level of direct
current of 126 μA or 100 μA/cm².

25   The test cell was in operation for four hours with each skin
sample. During operation, metoclopramide was iontophoretically
delivered from the donor solution through the cadaver skin into
the receptor solution. The receptor solution was sampled once
every hour over the four hour period. The entire volume (2 ml) of
30   receptor solution was collected and replaced with fresh solution
at each sampling point. The metoclopramide concentration in the
receptor solution was determined by UV absorbance at 310 nm using
a spectrophotometer manufactured by Hewlett Packard, of Palo Alto,
CA, Model No. 8452A. The average metoclopramide flux for each of
35   the four 1 hour periods was calculated and is presented in Figure

14

4. Each flux data point shown in Figure 4 was an average value from three skin specimens, all three specimens having been taken from the same cadaver.

5   The voltage for each skin sample was monitored throughout the experiment. A representative voltage was measured at 3.75 hours after start of operation for each skin sample and is recorded in Table 2. The power was calculated by multiplying the measured voltage at 3.75 hours by the applied current (i.e., 100

10   $\mu A/cm^2$). An average of the metoclopramide flux for hours three and four was calculated and is presented in Table 2. The ratio, as well as the average ratio, of average flux-to-power was then calculated and is presented in Table 2. From Table 2 it can be seen that back skin gave the highest average ratio of average

15   flux-to-power, followed by the abdomen and upper arm.

TABLE 2

Skin Site	Voltage* (Volts)	Power** (milliwatts)	Average Flux*** ($\mu g/cm^2 \cdot hr$)	Ratio of Average Flux-to-Power ($\mu g/cm^2 \cdot hr \cdot milliwatt$)	Average Ratio of Average Flux-to-Power ($\mu g/cm^2 \cdot hr \cdot milliwatt$)
Back	1.37	0.17	122.2	708	
	2.01	0.25	76.7	303	
	1.34	0.17	93.2	552	431
	1.92	0.24	67.7	280	
	1.52	0.19	65.7	343	
	2.05	0.26	103.7	401	
Chest	2.54	0.32	65.7	205	
	2.61	0.33	64.6	196	204
	2.63	0.33	69.9	211	
Abdomen	1.20	0.15	58.0	384	
	1.49	0.19	65.1	347	336
	1.72	0.22	60.0	277	
Hip/Thigh	2.46	0.31	50.7	164	
	2.12	0.27	81.4	305	222
	2.36	0.30	59.7	197	
Upper Arm	1.29	0.16	66.9	412	
	2.83	0.36	71.8	201	307
Forearm	1.56	0.20	69.2	352	
	3.03	0.38	58.9	154	230
	2.55	0.32	59.2	184	

* Measured voltage at 3.75 hours after start of operation.
** Power = voltage (at 3.75 hours) x current (= 100 $\mu A/cm^2$).
*** Average of the fluxes measured at 3 hours and 4 hours after start of operation.

15

COMPARATIVE EXAMPLE 1

The same equipment and procedures described in Example 1
were used to test human cadaver skin taken from the following
5   sites of the same cadaver tested in Example 1: abdomen, upper
arm, forearm, chest and hip/thigh. The average flux of
metoclopramide through these skin sites is also plotted in Figure
4. Figure 4 illustrates that there was a significantly higher
flux of metoclopramide through human back skin than through the
10   other tested human skin sites, i.e., the chest, abdomen,
hip/thigh, upper arm and forearm. In general, the flux of
metoclopramide through back skin was about 50% to 150% higher than
the metoclopramide flux through the other tested skin sites.

15   ## EXAMPLE 2

The electrical resistance of human skin to direct current
was tested in vivo using an iontophoretic delivery device. The
device included an anode electrode assembly and a cathode
20   electrode assembly which were secured on the skin of a subject.
Both electrode assemblies were connected by wires to an electric
current generator-controller which generated a constant level of
direct current. Each electrode assembly comprised a silicone ring
having an inner annulus filled with Dulbecco's phosphate buffer
25   saline (pH 7) gelled with 3% hydroxyethylcellulose. The skin
contacting area of the gel was 1.26 cm^2. The electrode assembly
also included a metallic electrode soldered to the connecting
wire. The anode was composed of silver while the cathode was
composed of Ag/AgCl. The electrode assemblies were secured to the
30   patient's skin using a pharmaceutically acceptable contact
adhesive. The generator-controller produced a constant direct
current level of 126 μA or 100 μA/cm^2. The devices were applied
to 12 human adult subjects, six male and six female. The devices
were applied to the back of each subject. Six of the twelve
35   subjects had the devices applied to the upper back while the

16

remaining six subjects had the devices applied to the lower back.
The devices were each applied for 15 minutes and the voltage was
measured at 0, 5, 10 and 15 minutes after application. The skin
resistance R_{dc} (kohm • cm^2) was then calculated using Ohm's law and
5   by assuming that the resistance of the device was very much less
than the skin resistance.

Both the average back skin resistance and the standard
deviation (i.e., variability) of the measurements is shown in
10 Figure 3.

COMPARATIVE EXAMPLE 2

The same procedures and apparatus described in Example 2
15 were used to test the same 12 human adult subjects, six male and
six female, at different skin sites including the lower arm, the
upper arm, the lateral side, the abdomen and the thigh. Both the
average electrical resistance and the standard deviation of the
measured resistance values (i.e., variability) is shown in Figure
20 3.

A comparison of the data plotted in Figure 3 shows that the
average electrical resistance of human back skin is at least about
40% lower than the electrical resistance of the next best skin
25 site evaluated (e.g., the lateral side site). In addition, the
variability in the electrical resistance of back skin is
substantially less than the variability in the measurements of
electrical resistance at the other tested skin sites.

EXAMPLE 3

30

The same 12 human subjects tested in Example 2 and
Comparative Example 2 were monitored for skin irritation and
tolerance to sensing the electric current at each of the skin

sites tested. At the end of each current application, the subjects were asked to grade skin sensation as follows:

5
        0 = no sensation
        1 = detectable and acceptable sensation
        2 = uncomfortable, but not unacceptable sensation
        3 = unacceptable sensation

10
Skin reactions at each of the tested skin sites were graded one hour, and again at 24 hours, following electrode removal. The skin reactions were evaluated according to the following scale.

Erythema

15
0 = None
1 = Barely perceptible redness
2 = Definite redness
3 = Beet redness

Extent of Erythema
20

0 = None
1 = Less than 50% of occluded area
2 = More than 50% of occluded area
3 = Less than 0.5 cm beyond occluded area
25
4 = More than 0.5 cm beyond occluded area

It was found that when the delivery devices were applied to the back skin, there was negligible irritation (i.e., the average
30
values for both erythema and extent of erythema were very much less than 1.0) of the back skin sites tested and the back skin sites exhibited no greater skin irritation than the other tested sites. Furthermore, the average sensation scores for each of the skin sites tested is presented below:
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Skin Site	Average Sensation Score
Upper back	0.50
Upper side	0.83
Lateral chest	0.67
Abdomen	0.42
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| Forearm | 0.75 |
| Upper arm | 0.50 |

Thus, the subjective evaluation of the 12 human subjects was
5   that the back skin sites provided a clearly acceptable level, and
one of the lowest levels, of sensation to the passage of a
constant level (i.e., 100 $\mu A/cm^2$) of electrical current.

The preceding examples illustrate preferred embodiments of
10   the present invention and are not to be construed as limiting.
The scope of the invention is defined and limited only by the
appended claims.

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Claims:

1.   A method of optimizing the transdermal flux of a
beneficial agent from an iontophoretic agent delivery device
5   through intact human skin and decreasing inter-patient skin
resistance variability, comprising:

optimizing transdermal flux while decreasing inter-patient
skin resistance variability by selecting a skin site on intact
10   back skin of the human;

placing the iontophoretic delivery device in agent
transmitting relation with the intact back skin site; and

15   iontophoretically delivering the agent through the back skin
at a pharmaceutically effective rate.

2.   The method of claim 1, wherein the device includes a
donor electrode assembly containing the beneficial agent, the
20   donor electrode assembly being placed in agent transmitting
relation with the intact back skin site.

3.   The method of claim 2, wherein the donor electrode
assembly is adhered in agent transmitting relation with the back
25   skin site using an ion-conducting adhesive.

4.   The method of claim 1, wherein the device includes a
donor electrode assembly containing the beneficial agent, a return
electrode assembly and an electrical power source electrically
30   connected to the donor and return electrode assemblies.

5.   The method of claim 4, including placing the donor
electrode assembly in agent transmitting relation with a first
intact back skin site and placing the return electrode assembly in
35   electrolyte transmitting relation with a second intact back skin

site, the second back skin site being spaced apart from the first
back skin site.

      6.   The method of claim 4, wherein the power source has a
5 fixed voltage.

      7.   The method of claim 6, wherein the fixed voltage is in
the range of about 1 to 10 volts.

10   8.   The method of claim 1, wherein the beneficial agent is
a drug.

      9.   The method of claim 1, wherein the beneficial agent is
selected from the group consisting of peptides, polypeptides,
15 proteins and macromolecules having a molecular weight of a least
about 300 daltons.

      10.   The method of claim 1, wherein the beneficial agent is
selected from the group consisting of insulin, growth hormones,
20 buserelin, leuprolide, LHRH, metoclopramide, fentanyl, lidocaine,
ketoprofen, sufentanil, terbutaline, droperidol, heparin,
interferon, scopolamine, testosterone, gonadorelin, ciclopirox
olamine, buspirone, calcitonin, cromolyn sodium, and midazolam.

25   11.   A method of optimizing transdermal flux of a
beneficial agent from an iontophoretic delivery device to a human
patient, the device including a donor electrode assembly
containing the beneficial agent, the donor electrode assembly
being adapted to be placed in agent transmitting relation to the
30 skin of the patient, a counter electrode assembly adapted to be
placed in electrolyte transmitting relation with the skin at a
location spaced apart from the donor electrode assembly and an
electric power source, the electrodes and the power source being
electrically connected and capable of forming a closed circuit
35 when the electrode assemblies are placed in agent transmitting and

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electrolyte transmitting relation to the skin of the patient,
comprising:

      optimizing the transdermal flux from the device while
5   decreasing inter-patient skin resistance variability by (a)
      selecting a skin site on intact back skin of the human patient,
      (b) placing the donor electrode in agent transmitting relation
      with the selected intact back skin site, and (c) iontophoretically
      delivering the agent through the back skin at a pharmaceutically
10   effective rate.

      12.   The method of claim 1 or 11, wherein the beneficial
      agent is co-delivered with a skin permeation enhancer through the
      intact back skin.
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      13.   The method of claim 11, wherein the power source
      comprises a battery having a voltage in the range of about 1 to 10
      volts.

20   14.   The method of claim 11, wherein the beneficial agent
      is a drug.

      15.   The method of claim 11, wherein the beneficial agent
      is selected from the group consisting of peptides, polypeptides,
25   proteins and macromolecules having a molecular weight of at least
      about 300 daltons.

      16.   The method of claim 11, wherein the beneficial agent
      is selected from the group consisting of insulin, growth hormones,
30   buserelin, leuprolide, LHRH, metoclopramide, fentanyl, lidocaine,
      ketoprofen, sufentanil, terbutaline, droperidol, heparin,
      interferon, scopolamine, testosterone, gonadorelin, ciclopirox
      olamine, buspirone, calcitonin, cromolyn sodium, and midazolam.

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17.   The method of claim 12, wherein the skin permeation
enhancer comprises a surfactant.
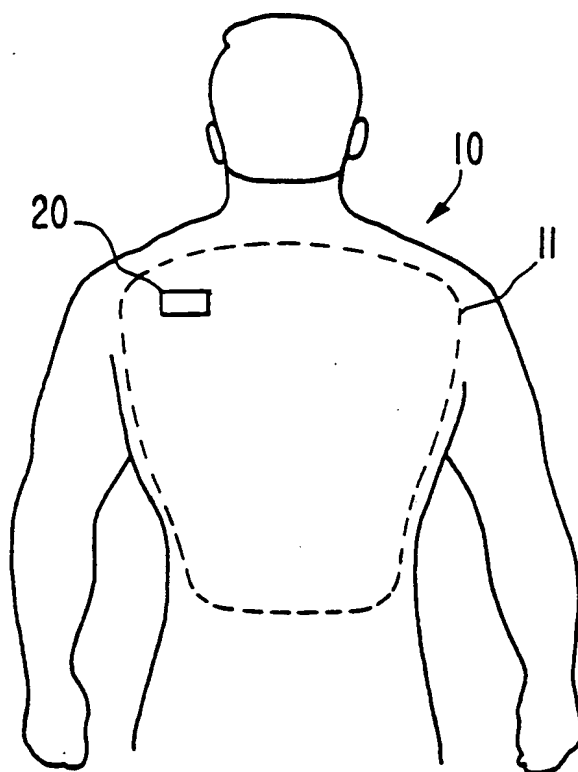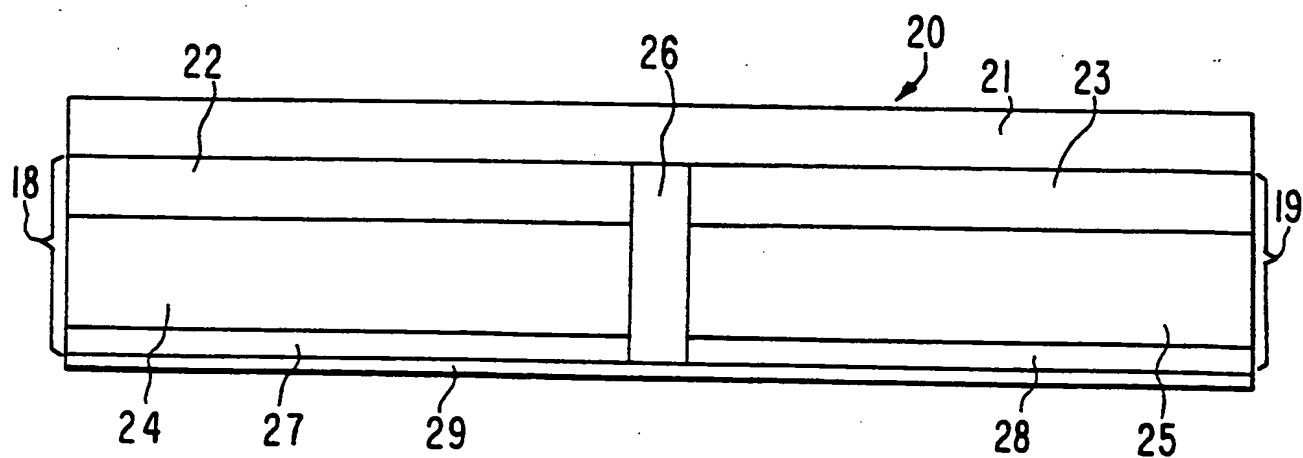
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FIG. I

FIG.2

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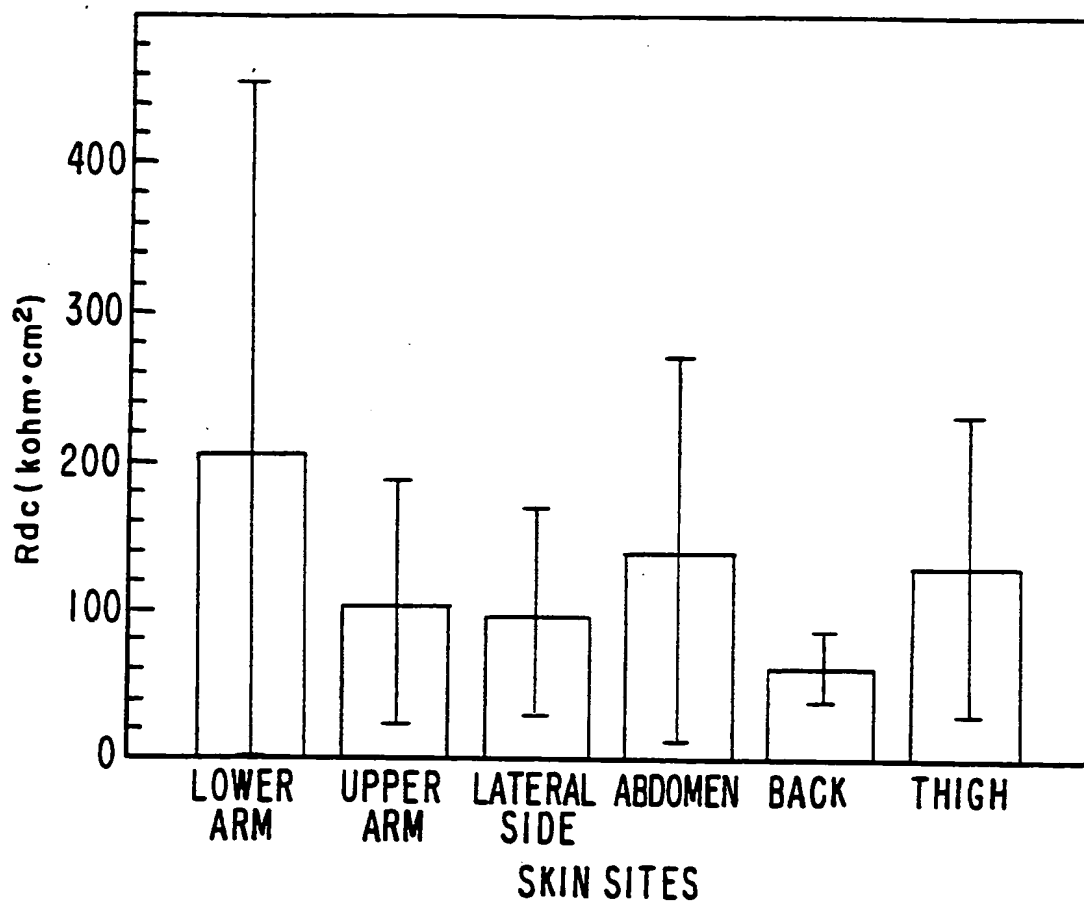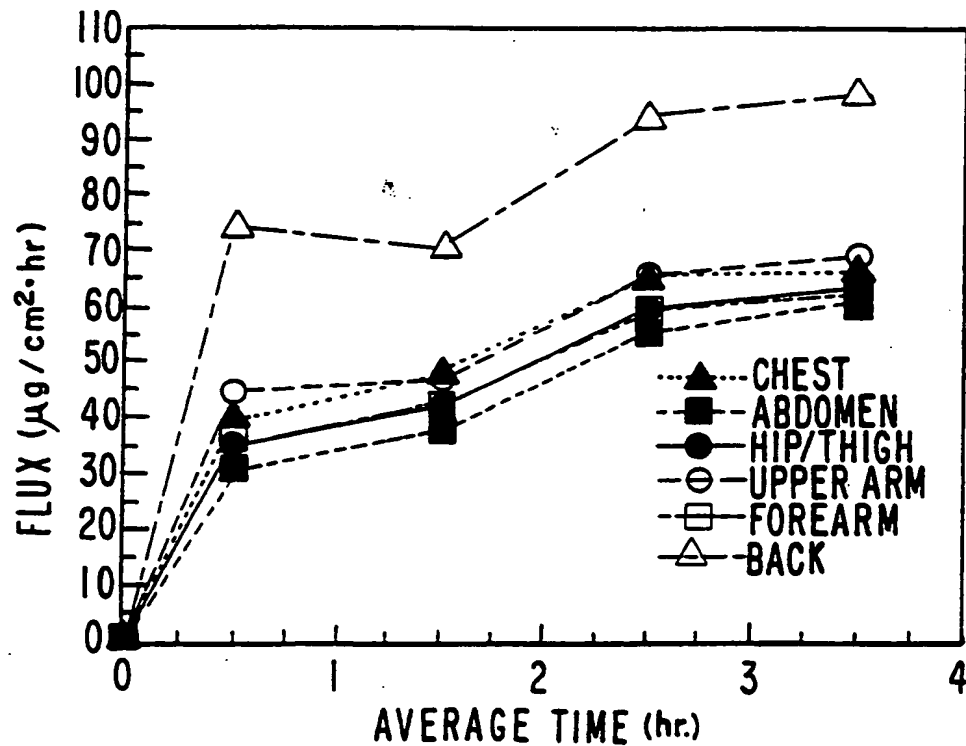
FIG.3

FIG.4